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Plasma homocysteine and cardiovascular risk in heart failure with and without cardiorenal syndrome

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Abstract

Introduction: Plasma homocysteine (Hcy) has been associated with an increased cardiovascular (CV) risk in patients with chronic heart failure (CHF). Thus, we investigated whether Hcy has a prognostic impact on CV events in CHF-patients with and without cardiorenal syndrome (CRS).
Methods: 161 patients with CHF were included in the present analysis. 94 patients had systolic (SD) (EF <40%) and 67 diastolic (DD) dysfunction (EF ≥ 40%). 60 had cardiorenal syndrome (CRS+ creatinine clearance < 60 ml/min). Mean ejection fraction was 38 ± 16% (n = 153) and mean VO2 max 19 ± 7 ml/min (n = 87).
Results: Homocysteine is significantly increased in patients with CHF (20 ± 7 μmol/l). The increase correlates not only with the severity of the disease (NYHA, EF, VO2max), but also with various metabolic (BNP, uric acid) and nephrologic parameters (creatinine, creatinine clearance). During follow-up (23 ± 37 months), patients with the highest homocysteine (≥ 20 μmol/l) passed away more often (p < 0.035) or decompensated more frequently (p < 0.004) than those with a low Hcy. In patients with CRS the rate of decompensation was significantly higher than in those without CRS (p < 0.0007).
Conclusions: Homocysteine is an important marker for an increased CV risk in patients with CHF. A homocysteine of ≥ 20 μmol/l is associated with a high risk to decompensate or to die (odds ratio 2.57). The presence of CRS is also associated with an increased CV risk (odds ratio 3.7) and predicts an adverse clinical outcome.

Keywords: Heart failure; Homocysteine; Cardiovascular risk factors; Cardiorenal syndrome

1. Introduction

Chronic heart failure (CHF) is a major health care problem and prevention of chronic heart failure is still an unsolved problem [1–3]. Numerous risk factors for CHF have been identified such as NYHA classification (New York Heart association), age, VO_2 at peak exercise, LVEF (left ventricular ejection fraction) and hemodynamic parameters such as LVEDD (left ventricular end-diastolic diameter), cardiac output, etc. [4,5].

More recently different biomarkers have been evaluated such as NT-pro-ANP (N-terminal pro-atrial natriuretic peptide), BNP (b-type natriuretic peptide) as well as NT-pro-BNP, CRP (c-reactive protein), catecholamines and uric acid [6–9]. From this group of cardiovascular risk (CV-risk) markers, BNP has emerged as best predictor for severity and outcome of patients with CHF [10,11,12]. Also inflammatory markers such as cytokines and Interleukin-6

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Table 1
Patients with systolic and diastolic dysfunction, respectively with and without cardiorenal syndrome.

Patient population		All	SD	DD	*p*	CRS +	CRS −	*p*
Number of patients		161	90	71		60	101	
Age (years)		56±14	56±13	56±14	ns	64±9	51±13	<0.001
BMI (kg/m2)		26±5	26±3	25±6	ns	25±4	26±7	ns
Female gender		22%	10%	37%	<0.001	17%	25%	ns
Heart rate		75±13	74±12	76±16	ns	75±12	75±14	ns
Blood pressure	systol	114±18	110±17	118±18	<0.05	113±19	114±18	ns
	diastol	75±11	72±87	77±55	<0.02	73±11	76±11	ns
Atrial fibrillation		25%	19%	32%	0.05	30%	22%	ns
Cardiovascular risk factors								
Positive family history		43%	44%	41%	ns	40%	45%	ns
Arterial hypertension		45%	44%	46%	ns	55%	40%	ns
Dyslipidemia		42%	49%	34%	0.05	50%	38%	ns
Smoking		14%	15%	11%	<0.04	7%	18%	ns
Diabetes mellitus		19%	19%	18%	ns	28%	13%	<0.02
Obesity		20%	21%	20%	ns	8%	28%	<0.001
Functional/Exercise capacity								
NYHA class *n*=156		2±0.8	2.1±0.7	1.9±0.7	ns	2.2±0.8	1.9±0.7	<0.04
6MWT (m) *n*=87		515±110	515±96	516±126	ns	497±117	524±107	ns
VO2max (ml/kg/min) *n*=87		19±7	19±6	19±8	ns	17±6	19±7	ns
EF (%) *n*=161		38±16	26±7	53±10	<0.001	32±14	41±16	<0.003
LVEDD (mm) *n*=161		59±11	65±9	51±10	<0.001	62±12	57±7	<0.02
Laboratory findings								
Hcy (umol/l)		19±7	20±7	18±7	ns	24±7	17±5	<0.001
CRP (mg/l) median		3	3	3	ns	3	2	ns
BNP (pg/ml)(*n*=156)median		146	256	61	<0.001	417	103	<0.001
Creatinine (umol/l) median		101	109	92	<0.02	137	86	<0.001
Creatinine clearance (ml/min)		74±33	70±30	81±35	<0.03	43±20	93±26	<0.001
Hb (g/l)		139±19	139±18	139±20	ns	131±20	144±17	<0.002
Urea (mmol/l) median		8.5	9.6	7.5	<0.02	14.1	6.7	<0.001
Uric acid (umol/l)		461±160	483±163	433±153	0.05	530±149	420±153	<0.001
Sodium (mmol/l)		139±3	139±3	140±3	<0.03	140±3	139±2	ns
Potassium (mmol/l)		4.2±0.5	4.3±0.4	4.1±0.5	<0.03	4.4±0.5	4.1±0.4	<0.002

BMI = Body mass index; NYHA: New York Heart Association; 6 MWT = 6 Minute Walking Test; VO2max = maximal VO_2 uptake at peak exercise; EF = Ejection fraction; LVEDD = left ventricular end diastolic diameter; Hcy = Homocysteine; CRP = C-reactive Protein; BNP = B-type natriuretic Peptide; Hb = Hemoglobin; SD = Systolic Dysfunction; DD = Diastolic Dysfunction; CRS = Cardiorenal Syndrome.
Inter-and intra-assay control values for all laboratory parameters:

Hcy	intra<1% (200 umol/l)	inter=3.9% (280 umol/l)
Uric acid	intra<1% (280 umol/l)	inter=1.3% (290 umol/l)
CRP	intra=2.8% (34 mg/l)	inter=4.6% (35 mg/l)
BNP	intra=9% (70 pg/ml)	inter=10% (70 pg/ml)
Creatinine	intra<1% (142 umol/l)	inter<1% (142 umol/l)
Urea	intra=1.3% (112 mmol/l)	inter=1.9% (116 mmol/l)
Sodium	intra<2%	inter=2%
Potassium	intra<2%	inter=2%
Hemoglobin	intra<2%	inter<2%

provide adjunct information for prognosis, especially when BNP is high [13]. New markers for CV risks have been tested such as hyperhomocysteinemia and severity of renal dysfunction (cardiorenal syndrome, CRS). Homocysteine (Hcy) had been shown to be an independent risk factor [14], causing an increase in oxygen stress and a decrease in endothelial function and thus, enhancing thrombotic events [15–18]. The purpose of the present study was to evaluate—in a retrospective analysis—the role of Hcy and CRS as CV risk factors for patients with chronic heart failure.

2. Methods

2.1. Patient population

Between 2003 and 2005, 288 patients with the diagnosis of CHF were screened for inclusion in the present study.